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## Hyposmia and Executive Dysfunction as Predictors of Future Parkinson's Disease: A Prospective Study

Mirthe M. Ponsen, MD,<sup>1\*</sup> Diederick Stoffers, MS,<sup>1,2</sup> Jos W.R. Twisk, PHD,<sup>3</sup>  
Erik Ch. Wolters, MD, PHD,<sup>1</sup> and Henk W. Berendse, MD, PHD<sup>1</sup>

<sup>1</sup>*Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands*

<sup>2</sup>*Department of Clinical Neuropsychology, VU University, Amsterdam, The Netherlands*

<sup>3</sup>*Department of Clinical Epidemiology and Biostatistics, VU University, Amsterdam, The Netherlands*

**Abstract:** Olfactory deficits and executive dysfunction are early and common symptoms in Parkinson's disease (PD). Previous studies have shown that hyposmia can be a first sign of PD. The aim of the present study was to determine which of three olfactory tests and two selected tests of executive function would be the best predictor of future PD over a 5 year period. In a cohort of 361 nonparkinsonian, non-demented first-degree relatives of PD patients, in whom alternative causes of olfactory dysfunction were excluded, we measured baseline performance on three olfactory and two executive function tasks. Five years from baseline, clinical neurological evaluation and/or a screening questionnaire,

sensitive to the presence of Parkinsonism, were used to detect individuals developing clinical PD. Our results show that in first degree relatives of PD patients worse performance on each of three olfactory processing tasks was associated with an increased risk of developing PD within 5 years, whereas performance on selected tests of executive dysfunction was not associated with an increased risk of developing PD. Interestingly, impaired odor discrimination was the best predictor for future PD. © 2009 Movement Disorder Society

**Key words:** Parkinson's disease; early diagnosis; olfaction; preclinical period; cognition

Olfactory loss is common in PD patients, with a reported prevalence of up to 80 to 90%.<sup>1,2</sup> The olfactory deficit in PD occurs even in early stage, untreated PD patients and includes impairments in several modalities, i.e., odor detection, discrimination and identification.<sup>3,4</sup> In a cohort of first degree relatives of PD patients, we were able to demonstrate that unexplained hyposmia can be a first sign of PD.<sup>5,6</sup> These findings were later confirmed by an independent study in a population of individuals with idiopathic hyposmia.<sup>7,8</sup> Also, in a population-based study, hyposmia was recently found to be associated with an increased risk of future PD.<sup>9</sup>

The sense of smell can be dissected into at least three different components.<sup>10</sup> Odor detection testing measures the lowest concentration of an odorant that can be perceived by a subject. Odor identification testing involves the perception and naming of an odor presented. An odor discrimination task measures the ability to differentiate between a set of odorants. So far, the predictive value of olfactory testing for a later diagnosis of PD has not been compared between tests of different olfactory modalities, such as odor discrimination and odor identification.

Early-stage cognitive disturbances in PD include executive dysfunction, visuo-spatial impairments, and disturbances of working memory.<sup>11</sup> Motor perseveration and a decrease in sequential visuo-spatial memory span, most likely reflecting executive dysfunction, appear to be very early features of PD.<sup>12–14</sup> In the MPTP-treated primate, an animal model of PD, executive deficits have been found before the appearance of clinical motor disturbances,<sup>15</sup> suggesting that these impairments may be a feature of the pre-motor stages

\*Correspondence to: Dr. M.M. Ponsen, Department of Neurology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: mm.ponsen@vumc.nl

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of PD. Indeed, in first-degree relatives of PD patients the incidence of PD-like executive dysfunction is increased, possibly as a manifestation of pre-motor PD.<sup>16</sup> However, the predictive value of executive dysfunction for the future development of PD has never been assessed prospectively.

The aim of the present study was to determine the association between the risk of developing clinical PD over a five-year period and baseline performance on tests of olfactory and executive function as part of an ongoing prospective cohort study in first degree relatives of PD patients. A further purpose of this study was to determine which of the individual olfactory or executive function subtests would be associated with the highest risk of future PD.

## SUBJECTS AND METHODS

### Study Population/Subjects

At baseline, the study population consisted of 361 first-degree relatives (285 children, 73 siblings, and 3 parents) of patients with sporadic PD. Subjects were recruited partly from the general population and partly from family members of patients at the outpatient clinic for movement disorders of the VU University Medical Center (VUMC).

As described previously,<sup>5</sup> relatives were included when they fulfilled the following criteria: (1) clinical diagnosis of PD in the affected relative made by a VUMC neurologist ( $n = 23$ ) or established retrospectively using information obtained from the unaffected relatives ( $n = 338$ ); a retrospective diagnosis in the affected relative required a combination of parkinsonian symptoms and signs as defined by the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) criteria,<sup>17</sup> responsive to dopaminergic medication; (2) absence of a history of other (neuropsychiatric) disorders or conditions known to influence olfactory function; (3) no medication that might influence dopamine transporter binding and/or olfactory function; (4) absence of parkinsonism as defined by the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) criteria<sup>17</sup>; (5) Unified Parkinson's Disease Rating Scale (UPDRS) motor score  $<5$ ; (6) Cambridge examination for mental disorders (CAMCOG) orientation and memory section score  $>26$ . All participants gave written informed consent; the protocol of the study was approved by the Health Council of The Netherlands and the local medical ethical committee of the VUMC.

### Baseline Testing

At baseline, all 361 subjects were submitted to a combination of three olfactory processing tasks and two executive function tasks known to be disturbed in early stage PD patients. The olfactory tests included an odor detection, an odor discrimination and an odor identification task.<sup>5</sup> The odor detection task was adapted from a task developed by Doty et al.<sup>18</sup> The odor discrimination task used was developed at the University Medical Center Utrecht.<sup>19</sup> A modified version of the 12-item Cross-Cultural Smell Identification Test (CC-SIT),<sup>20</sup> adapted to the Dutch population, was used to assess odor identification.

The first executive function task was the Vienna perseveration task (Dr. G. Shuhfried Ges.m.b.H, Mödling, Austria) in which perseveration in the generation of random motor behavior is examined.<sup>13</sup> The second task was the Vienna adaptation of the Corsi Block-Tapping Task (Dr. G. Shuhfried Ges.m.b.H, Mödling, Austria) used to assess sequential visuo-spatial memory span.<sup>12</sup>

### Five Year Follow-Up

Five years after baseline testing, 354 subjects were available for follow-up. Seven relatives were lost to follow-up, six of whom died. For one relative, we were unable to trace his current address. A subgroup of seventy-four relatives was selected at baseline for additional dopamine transporter SPECT scanning as part of the follow-up evaluations.<sup>5</sup> This selected group was seen at the outpatient clinic for movement disorders of the VUMC and subjected to a full clinical neurological examination. Follow-up of the majority of relatives ( $n = 280$ ) was performed by means of a mail questionnaire sensitive to the presence of Parkinsonism (see below). Eighteen relatives with possible Parkinsonism according to the questionnaire were subsequently invited to the outpatient clinic for a full neurological evaluation.

Clinical neurological examinations were carried out by a movement disorders specialist and included a screening neurological examination and a specific assessment to detect the presence of Parkinsonism as defined by the UK-PDSBB criteria.<sup>17</sup> Motor function was rated by means of the motor section of the UPDRS. Individuals that had already developed clinical PD prior to the scheduled 5 year follow-up evaluation and were already using medication were tested "off"-medication, i.e. at least 12 hours after their evening dose.

The mail questionnaire used was a Dutch translation of a validated screening questionnaire for PD, as

**TABLE 1.** Demographics and scores on olfactory processing tasks and cognitive tasks (mean  $\pm$  SD), measured at baseline

	PD (n = 5)	No PD (n = 348)	Lost to follow-up (n = 8)
Sex (male / female)	3/2	150/198	4/4
Age (mean $\pm$ SD)	62.4 $\pm$ 6.3	58.7 $\pm$ 6.5	58.6 $\pm$ 8.1
Odor discrimination	13.6 $\pm$ 4.8	21.0 $\pm$ 4.4	20.8 $\pm$ 3.7
Odor detection	9.8 $\pm$ 1.3	13.3 $\pm$ 2.1	14.4 $\pm$ 1.2
Odor identification	7.2 $\pm$ 2.1	9.7 $\pm$ 1.7	10.6 $\pm$ 0.9
Corsi block task	5.6 $\pm$ 0.9	5.3 $\pm$ 0.9	5.5 $\pm$ 1.3
Perseveration task	23.6 $\pm$ 8.4	23.2 $\pm$ 10.1	18.9 $\pm$ 7.2

described previously.<sup>6</sup> This mail questionnaire comprised nine symptom questions and an extra question to establish whether any physician had made a diagnosis of PD over the course of the follow-up period. Three or more positive responses to the symptom questions, as well as a positive response to the additional question, were considered indicative of possible Parkinsonism. Individuals with possible Parkinsonism according to the questionnaire were submitted to a structured clinical work-up, comprising a standard history taking and a neurological examination including the UPDRS motor score. The structured clinical work-up was performed by a movement disorders specialist, who was not involved in the baseline screening and was blinded to the baseline olfactory and executive function test scores.

The data were analyzed in SPSS (SPSS inc., Chicago, IL, U.S.A.). Cox-regression analysis (univariate and multiple) was used to calculate hazard ratios for developing PD. The relation with olfactory and executive function subscores was analyzed using a forward stepwise method (0.05 probability of F for entry, 0.10 for removal of a determinant from the regression equation) using three olfactory function subscores (odor detection, odor discrimination, odor identification), two executive function subscores (visuo-spatial memory span, perseveration) as well as age and sex in the initial regression equation.

## RESULTS

Five years from baseline testing, five relatives had developed clinical PD as defined by the UK-PDSBB criteria. Initial clinical (motor) symptoms appeared 9 to 52 months (median 15 months) after baseline testing. Five years from baseline, "off"-medication UPDRS motor scores were 13, 16, 18, 29, and 52. Three relatives were using antiparkinsonian medication (dopamine-agonist and/or levodopa), and had a good clinical response. Of the other 349 relatives available for follow-up, none fulfilled UK-PDSBB criteria for a parkinsonian syndrome. This included the relatives in the questionnaire group, 18 of whom had 3 to 7 (out of nine) positive responses to the screening questionnaire. Clinical neurological evaluation did not reveal a parkinsonian syndrome in any of these 18 relatives.

The olfactory processing task scores in the five relatives that had developed PD were significantly lower than in the healthy subjects. No significant difference between groups was found for the scores on the executive function tasks. Mean  $\pm$  SDs for olfactory and executive function testing are listed in Table 1.

Univariate Cox regression analysis of the test scores on the individual olfactory processing tasks revealed a significantly increased risk of developing PD with lower scores for each task (Table 2). The hazard ratio for odor discrimination was 0.73, which indicates that when the odor discrimination score decreases with one point, the risk of developing PD increases with 0.73. The hazard ratios for odor detection testing and odor identification testing were 0.60 and 0.62, respectively. When the individual olfactory processing tasks were combined into a multiple Cox-regression analysis, the odor discrimination task was the best predictor for future PD. The contribution of the odor detection task was limited (trend), whereas the baseline score on the odor identification task did not have any additional value in predicting the future development of PD. Performance on the two executive function tasks was not associated with the risk of developing clinical PD.

**TABLE 2.** Cox regression analysis

	Univariate		Multivariate	
	Hazard ratio (c.i.)	P	Hazard ratio (c.i.)	P
Odor discrimination	0.728 (0.606–0.875)	0.001	0.810 (0.665–0.986)	0.036
Odor detection	0.598 (0.436–0.819)	0.001	0.724 (0.501–1.045)	0.084
Odor identification	0.622 (0.463–0.835)	0.002	–	–
Corsi block task	1.357 (0.584–3.151)	0.477	–	–
Perseveration task	1.005 (0.926–1.090)	0.912	–	–

## DISCUSSION

In this prospective study involving first-degree relatives of PD patients, worse performance on each of three olfactory processing tasks was associated with an increased risk of developing PD within 5 years. Among the olfactory tests used, odor discrimination testing appeared to be the best predictor for the future development of PD. Baseline executive function, as measured using two tasks known to be impaired in early-stage PD patients,<sup>12–14</sup> did not have any predictive value for a later diagnosis of PD in this population.

The first indications that an impaired sense of smell might be taken as an early sign of the development of PD were derived from two studies observing olfactory dysfunction in asymptomatic relatives of patients with either familial or sporadic forms of PD.<sup>21,22</sup> Subsequently, the baseline evaluation of the present cohort of first degree relatives of PD patients revealed a sub-clinical degeneration of the nigrostriatal dopaminergic system in some hyposmic, but otherwise asymptomatic, first-degree relatives of PD patients.<sup>5</sup> Two-year follow-up data of this same cohort showed that unexplained olfactory loss can indeed be a first sign of PD.<sup>6</sup> This notion was later confirmed in an independent study in individuals with idiopathic hyposmia.<sup>8</sup> Recently, the above observations in selected populations were corroborated in a population-based study of elderly men using a short test of odor identification.<sup>9,23</sup> The present five-year follow-up data of our cohort of first-degree relatives of PD patients, confirm the increased risk of future PD conveyed by olfactory loss over a five-year period and, in addition, show that odor discrimination testing may be the better test to use.

The recently published data from the Honolulu-Asia Aging Study<sup>9</sup> have shown that impaired olfaction was not a strong predictor of PD when follow-up time from olfactory testing to the development of PD was beyond 4 years. This might imply that olfactory deficits in PD begin 4 years or less before the appearance of classic motor features. This notion is supported by the observation by Marras et al.<sup>24</sup> in a population of twins that impaired olfaction was not a good indicator of future PD more than 7 years prior to the development of the typical motor signs. In the present five-year follow-up study the longest interval between baseline olfactory testing and the development of clinical PD was 52 months (4.3 years). Similar results were found by Haehner et al.<sup>8</sup> However, follow-up data beyond a 5 year period are necessary before firm conclusions can be made about the length of the pre-motor period characterized by hyposmia.

Previously, Doty et al.<sup>25</sup> and Lotsch et al.<sup>10</sup> have reported that olfactory test scores on different tasks (identification, discrimination, and detection) load on a single primary component in a principle component analysis. Apparently, the available olfactory tests share a certain aspect of olfactory function. Yet, this does not imply that odor detection, identification, and discrimination are fully equivalent olfactory modalities. The results of the present study would seem to support that different olfactory tasks may tap into different cerebral functions. Several imaging studies provide additional anatomical evidence for this concept, demonstrating that olfactory functions are mediated by common as well as task-specific regions in the brain.<sup>26,27</sup>

Neuropsychological investigations in PD patients have shown specific executive impairments in the initial phase of the disease.<sup>12,13</sup> It is therefore tempting to speculate that executive function deficits may also occur in the pre-motor stage of PD, a notion supported by the observation in the MPTP monkey that executive function deficits are present before the onset of clinical motor disturbances.<sup>15,16</sup> In the present study, baseline executive function in asymptomatic first-degree relatives of PD patients was not associated with the risk of developing PD within 5 years. This would seem to argue against the presence of executive impairments in the pre-motor stage of PD and, in addition, imply that tasks of executive function are not helpful in the pre-clinical diagnosis of PD. However, it should be emphasized that we used only two specific tasks involving executive functions. Therefore, we can not exclude that other tests of (executive) cognitive function might serve better as predictors for the development of future PD.

The present results support the existing evidence that olfactory processing tasks might be useful as part of early diagnostic strategies in PD. Among the olfactory tests used, the odor discrimination test appeared to be the best predictor of future PD. This is somewhat unexpected since in previous studies, including a recent study comparing odor identification and odor discrimination deficits in PD patients, we found impaired odor identification performance to be more prevalent than a deficit in odor discrimination.<sup>3,28</sup> Moreover, odor identification testing differentiated better between PD patients and healthy subjects than odor discrimination. In the latter study, contrary to the present study, elements of the Sniffin' Sticks test battery were used, including a 16 item discrimination task. In the present study, the discrimination task comprised 32 items.



Therefore, differences in the olfactory tasks used as well as the different number of items in the discrimination task might have contributed to the apparently contradictory results. Clearly, the exact value of the individual aspects of olfactory function in predicting future PD needs further study.

A limitation of this study is that we used a selected sample of relatives of PD patients, excluding subjects with a history of other disorders or conditions known to influence olfactory function. Therefore, our results are not necessarily applicable to the general population. In addition, only five individuals of 361 first degree relatives of PD patients developed clinical PD during our prospective study. Although this number of cases corresponds to the expected incidence of new cases over the 5 year follow-up in a cohort of this size, a larger baseline population and hence a higher number of PD patients would provide a more accurate predictive value for olfactory and executive function testing. Another limitation is that we tested only two specific aspects of executive function; i.e. motor perseveration and sequential visuo-spatial memory span. It could well be that other tasks measuring similar or different aspects of executive function have better predictive value for the development of PD. On the other hand, early stage PD patients were impaired on these particular tasks in previous studies.<sup>12,13</sup>

An important strength of this study is its prospective, longitudinal design. Furthermore, in spite of the long interval between baseline evaluation and five-year follow-up, only very few individuals were lost to follow-up.

In conclusion, we found that in a cohort of first-degree relatives of PD patients worse performance on each of three olfactory processing tasks was associated with an increased risk of developing PD within 5 years, whereas executive dysfunction was not associated with an increased risk of developing PD within 5 years. Impaired odor discrimination appeared to be the best predictor of the future development of PD.

**Author Roles:** *M.M. Ponsen*: Research project: Organization, Execution; Statistical Analysis: Execution; Manuscript: Writing of the first draft; *D. Stoffers*: Research project: Organization, Execution; Statistical Analysis: Execution; *J.W.R. Twisk*: Statistical Analysis: Design, Review and Critique; *E.Ch. Wolters*: Research project: Conception; Manuscript: Review and Critique; *H.W. Berendse*: Research project: Conception, Organization; Statistical Analysis: Review and Critique; Manuscript: Review and Critique.

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